IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Clarence N. Ahlem, et al.
App. No.	: 09/820,483
Filed	: March 29, 2001
Title	: Immune Modulation Method Using Steroid Compounds
Examiner	: Elli Peselev
Docket No.	: 202.3
Customer No.	: 26,551
Confirmation No.	: 5293

DECLARATION

Mail Stop Amendment
Assistant Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Christopher L. Reading, declare as follows:

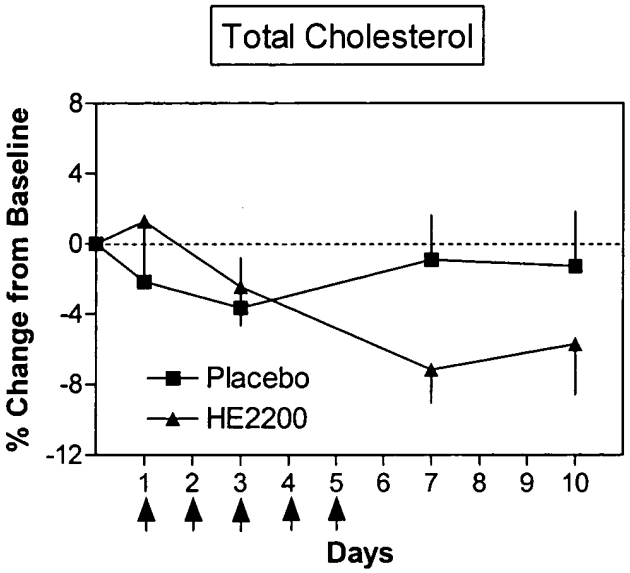
1. I am a co-inventor of subject matter contained in the above-referenced patent application and an employee of the assignee of this patent application. I have read and understood the office action that was mailed on May 14, 2004 and the pending claims. I have been engaged in the evaluation and development of therapeutic agents and treatment methods for over 20 years, which includes 4 years of experience with preclinical and clinical development of steroid compounds. My curriculum vita is included with this declaration.

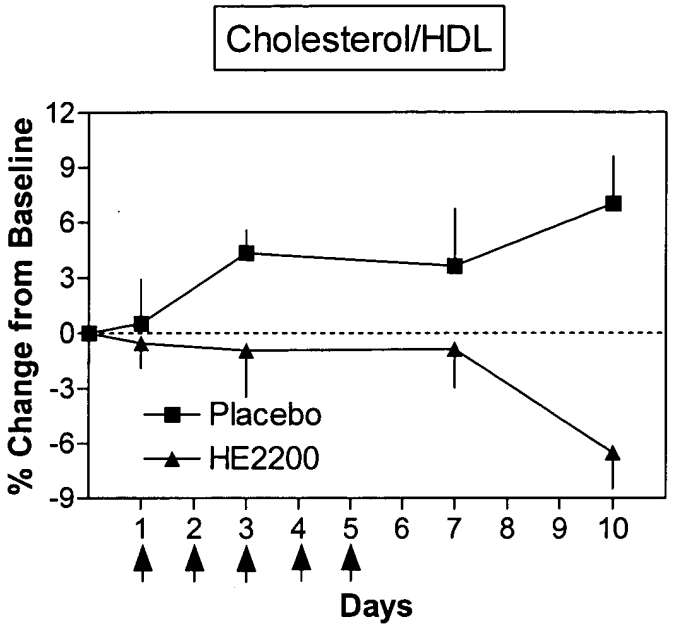
2. The statements in paragraphs 5-6 are based on my analysis of the data in paragraphs 3-5, the references cited below and on discussions with persons who were involved in obtaining the data in paragraphs 3 and 4.

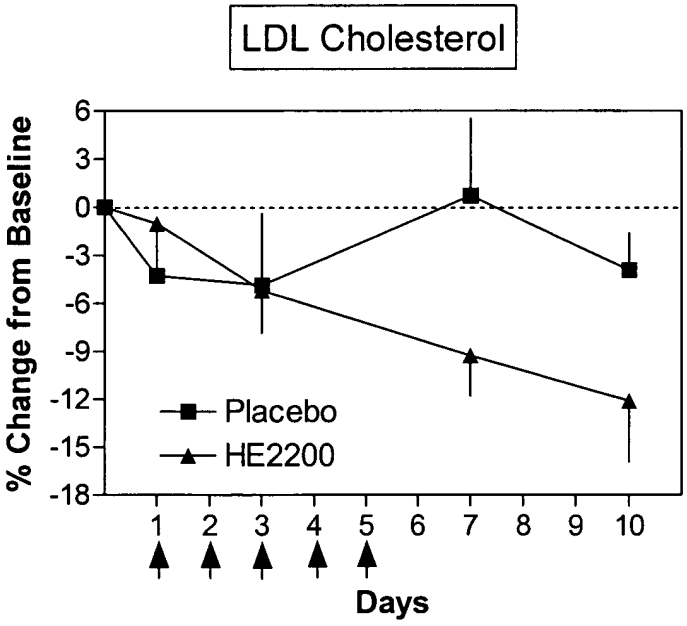
3. The compound 3β,7β,17β-trihydroxyandrost-5-ene (referred to as "HE2200") was administered to humans in three protocols. In the first protocol, HE2200 was administered to 23 healthy adult and elderly volunteers by buccal delivery to examine various biological response parameters such as tolerance, safety and effects on immune markers. Eight patients received placebo buccal tablets to generate an untreated control group. Two HE2200 dose levels, 25 mg/day for 5 consecutive days and 100 mg/day for 5 consecutive days, were used in for this phase I clinical study, followed by 54 additional days of further observation without administration of the compound. During the five day dosing period, the patients were kept on a low fat intake diet. In the second protocol, HE2200 was administered to 71 dyslipidemic patients and placebo was administered to 20 dyslipidemic patients. Of the 71 treated patients, 66 completed the entire protocol. For 6 weeks before dosing with HE2200 started, all 71 patients had been on a step 2 American Heart Association lipid-lowering diet and had discontinued the use of lipid lowering agents, such as statins. In this phase II study, the patients received daily doses of 25 mg or 100 mg of HE2200 or placebo for four weeks. Patients were monitored for an additional two weeks to get biological parameters, a lipid panel profile and other information. In the second protocol, HE2200 at 25 mg/day or 100 mg/day did not have a statistically significant effect on lipids or cholesterol in the treated patients compared to the controls. By contrast, treated patients in the first protocol experienced at 5 days after dosing had ended showed a statistically significant trend ($0.05 < p \leq 0.10$) in lipid parameters for the 100 mg treatment group compared to the untreated patients. Changes in the lipid profiles for the 25 mg treatment group in either protocol were not significantly changed compared to the placebo groups. By the end of the observation period, lipid profiles in HE2200 treated patients had returned to baseline levels.

4. In particular for the first protocol, a statistically significant decrease ($p = 0.0158$) was observed in the 100 mg treatment group versus the placebo vehicle group for the total cholesterol/HDL ratio using pooled adult and elderly age

cohorts in the analysis. This data is shown in the second graph below. A decrease in the total cholesterol:HDL ratio is a useful change, which is associated with a reduced probability of atherosclerotic disease. D. Kothapalli et al., *J. Clinical Investigation*, 113:609-618, 2004, newly cited. I believe that the effect of HE2200 on reducing the total cholesterol:HDL ratio was not predictable.

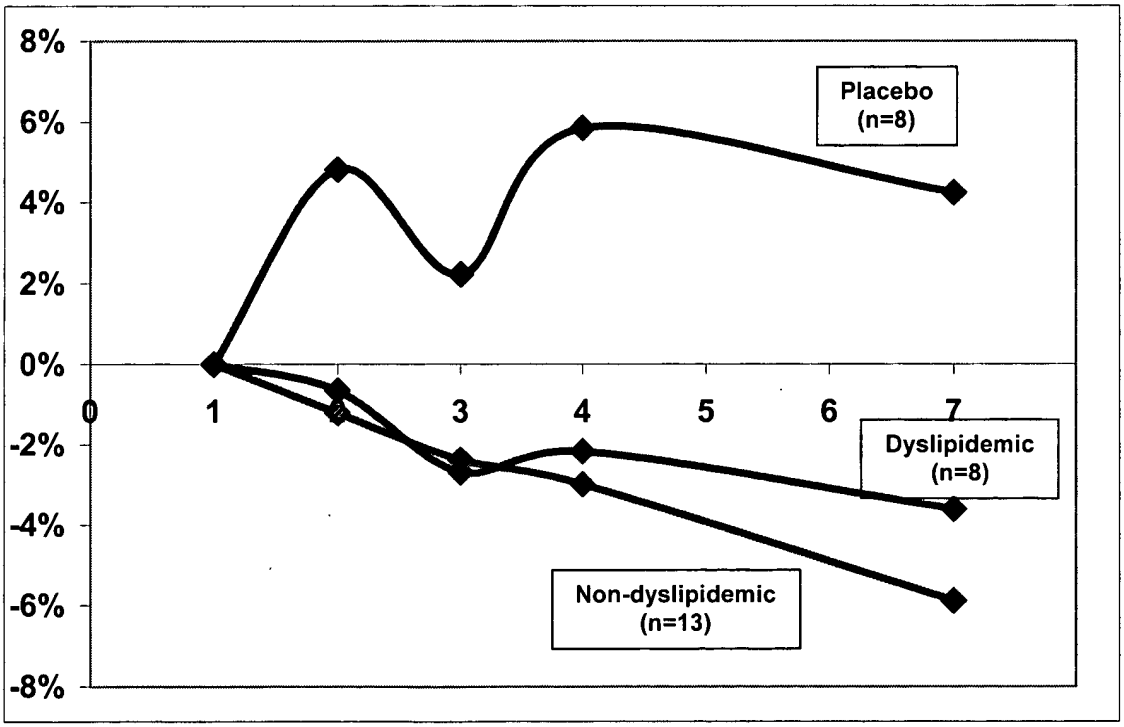



Cholesterol/HDL
% Change from Baseline
12
9
6
3
0
-3
-6
-9
Placebo
HE2200
1 2 3 4 5 6 7 8 9 10
Days

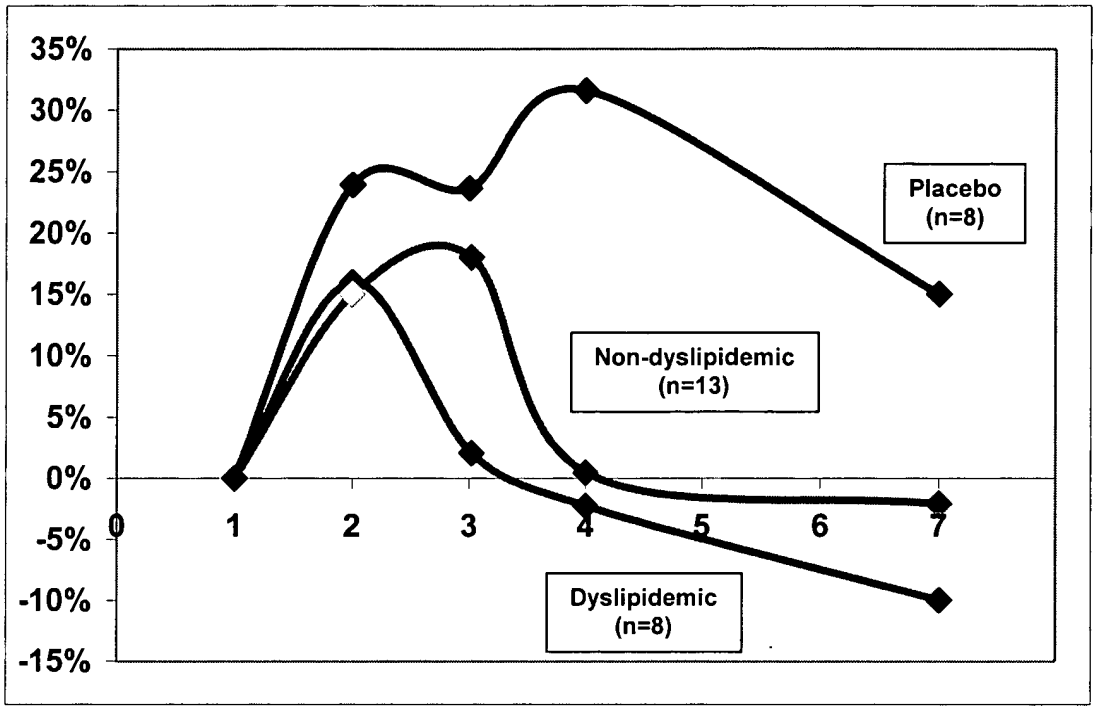

LDL Cholesterol
% Change from Baseline
6
3
0
-3
-6
-9
-12
-15
-18
Placebo
HE2200
1 2 3 4 5 6 7 8 9 10
Days

5

5. In the third protocol, healthy volunteers received 3 consecutive daily injections of either 50 mg/day or 100 mg/day of HE2200. Placebo controls received 3 consecutive daily injections of the vehicle without HE2200. There were 8 placebo treated control patients, 8 dyslipidemic patients and 13 non-dyslipidemic in this phase I clinical study. In this protocol there was a significant decrease in the total cholesterol:high density cholesterol ratio ($p = 0.048$, Mann-Whitney analysis) for the combined treated groups at day 7, which was 4 days after dosing ended. The prolonged effect on lipid profiles was potentially due at least in part to the long observed half-life or persistence for the drug, which was greater than 50 hours in blood. This long half-life was also observed in patients that received HE2200 by buccal dosing described above.



Decreased total cholesterol:high density cholesterol ratio at day 7 (p = 0.048)



Triglyceride lowering trend at day 7 (0.1 ≤ p > 0.05)

The results shown in the two graphs above show data % change from baseline for the 8 placebo controls compared to all patients in the 50 mg and the 100 mg treated groups (n = 21). In addition to the triglyceride lowering trend, both treated groups also showed a trend (0.1 ≤ p > 0.05) for reduced total cholesterol and for reduced LDL cholesterol at day 7, which was 4 days after the last of the three HE2200 doses. In this protocol, dyslipidemic patients (n = 4) in the 100 mg treated group had a decreased LDL cholesterol of about 18% at day 7, while non-dyslipidemic patients in the 100 mg treated group (n = 7) had a decrease from baseline of about 9% at day 7 and the placebo group (n = 8) had a decrease of about 5% at day 7. These changes are all consistent with lipid profile changes that one would want in a treatment for cardiovascular diseases like elevated cholesterol or atherosclerosis.

6. Given the results discussed above, I believe that HE2200 and related compounds will have therapeutic activity in improving lipid profiles, particularly where patients have a dyslipidemia condition. The two main sources of cholesterol in humans are *de novo* synthesis in the liver and intake from food. Each source contributes significantly to the total cholesterol in circulation. E.J. Smart et al., *Proc. Natl. Acad. Sci.* USA 101:3450-3455 2004, newly cited. The activity of HE2200 in reducing cholesterol as seen in the first protocol is consistent with a mechanism of action that is partially or largely based on its capacity to interfere with or inhibit the uptake of cholesterol from food. Particularly striking was the 10-12% decrease in LDL cholesterol that was observed after 5 days of dosing in the first protocol. The approved drug ezetimibe is used in combination with a statin (atorvastatin) to treat hypercholesterolemia. Ezetimibe works by inhibiting cholesterol uptake from food. C. M. Ballantyne et al., *Intl. J. Clin. Practice*, 58:653-658, 2004, newly cited. When used as a monotherapy in a 12-week study, ezetimibe reduced low-density lipoprotein cholesterol by about 18-20%. R.H. Knopp et al., *Intl. J. Clin. Practice*, 57:363-368, 2003, newly cited. The full range of biological activity and potency for HE2200 cannot be observed with the data discussed above. However, given the limited duration of dosing with HE2200 described above and its effect in generally improving lipid and cholesterol profiles, I believe that compounds such as HE2200 will have useful therapeutic activity. This activity is potentially similar to ezetimibe, in treating conditions such as atherosclerosis and elevated cholesterol.

7. I hereby declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such false statements may jeopardize the validity of the application or any patent issued thereon.

Date: Nov 15, 2004 By: Christopher L. Reading

Christopher L. Reading